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Short Communication

Long-term improvement of lung clearance index in patients with mild cystic fibrosis lung disease: Does hypertonic saline play a role?

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Abstract

To assess whether long-term inhalation with hypertonic saline is able to halt the progression of mild CF lung disease, we analysed longitudinal data of lung clearance index (LCI) and spirometry. A total of 34 patients with mild lung disease ($FEV_1 \geq 70\%$ of predicted) had at least one LCI result before and ≥2 LCI measurements after start of hypertonic saline (HS) therapy. After a mean follow-up of 39.7 (SD 7.4) months after starting HS, LCI improved significantly from 7.89 (SD 1.35) at baseline to 6.96 (SD 1.03), and 19/34 patients had a normal LCI value at the last measurement. No decrease in mean FEV_1 was observed. Thus, ventilation inhomogeneity can improve in patients with mild lung disease.

1. Introduction

Despite near-normal spirometry, patients with mild cystic fibrosis (CF) lung disease often show structural abnormalities on high-resolution chest tomography scans (HRCT) [1]. When investigated with sensitive methods such as the multiple breath washout (MBW) technique, ventilation inhomogeneity is found in many subjects with normal FEV_1, as reflected by abnormal lung clearance index (LCI) results [2,3].

Lung clearance index measurements were introduced at our centre in 2007, primarily for mildly affected patients. In patients with a forced expiratory volume (FEV_1) >80% of the predicted normal value we observed that LCI was a surrogate parameter for structural lung abnormalities on high-resolution CT scans [4]. After the initial study, serial measurements of lung clearance index and FEV_1 showed a relatively stable longitudinal course of ventilation inhomogeneity in these patients with mild lung disease [5].

Between 2007 and 2009, hypertonic saline (HS) was added to the treatment regimen of most of our patients, after two trials had shown its efficacy and safety [6,7]. The present retrospective evaluation compares the two lung function parameters, FEV_1 and LCI, during long-term inhalation of hypertonic saline. Most LCI measurements were obtained during a prospective observational study [5]. We hypothesised that the introduction of HS would stabilise lung function and that the LCI would be more suitable than FEV_1 to detect these changes.

2. Patients and methods

Of the 160 patients treated at our centre in 2011, 96 patients had at least one MBW measurement. There were 34 patients with $FEV_1 \geq 70\%$ of the predicted value who had at least one

Abbreviations: CF, cystic fibrosis; ECFS, European Cystic Fibrosis Society; HS, hypertonic saline; LCI, lung clearance index; MBW, multiple breath washout; SF6, sulfur hexafluoride

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LCI result before and at least two LCI measurements after the start of hypertonic saline therapy.

Patients received chronic CF treatment according to established guidelines and our own standardised procedures [15,16]. Commencing in 2007, we started prescribing hypertonic saline (HS). Treatment was initiated during a physiotherapy session under the supervision of a respiratory therapist, starting with a concentration of 3%. Thereafter, most patients inhaled a 5% saline solution twice daily via a Pari eFlow rapid inhaler for chronic therapy. After a 6% saline solution became commercially available, patients were switched to the higher concentration solution. No other systematic treatment changes relevant for this patient cohort were introduced between 2007 and 2012.

Patients were examined during a routine visit to the CF outpatient clinic when clinically stable. They were advised not to inhale any medication in the morning. Multiple breath washout (MBW) measurements were performed after the medical consultation and before spirometry. Lung clearance index was measured when patients were clinically stable, using a prototype of the EasyOne Pro™ LAB from ndd Medizintechnik AG, Zurich, Switzerland [4]. All MBW measurements were performed by the same staff using the same equipment [12]. Values were analysed as described earlier, using appropriate quality control procedures and reference values [12]. The same equipment with sulfur hexafluoride (SF6) as a tracer gas was used throughout the whole observation period, which ended in March 2012, when nitrogen was introduced as a washout gas. Spirometries were performed using a Master Screen Bodyplethysmograph (Erich Jaeger, Germany) [8,9].

The sequence of MBW measurements did not follow a regular pattern in relation to the start of HS, and some patients had more assessments than others. To assure a reasonable comparison of MBW results, we analysed three time points for each patient: the last measurement before starting HS (pre), and the first and the last measurements after commencing HS inhalations (first post and last post, respectively). We tested the intraindividual differences in LCI values between these time points and the differences in FEV_1 between 3 years pre and post starting HS by performing paired *t*-tests with GraphPad Prism 6.04, GraphPad Software Inc., La Jolla, CA, USA.

Table 1
Demographic and clinical data before commencing hypertonic saline.

	Mean	SD
Sex (male/female)	19:15	
Age (years)	15.6	9.2
	(range: 6 to 53 years)	
LCI	7.85	1.35
Functional residual capacity (FRC)	1.67	0.82
FEV_1 (% predicted)	94.8	17.0
Forced vital capacity (FVC) (% predicted)	95.0	14.6
MEF_{25} (% predicted)	76.7	29.9

3. Results

Demographic and clinical data of the 34 patients before starting HS are shown in Table 1. Despite mostly normal FEV_1, two-thirds of the patients (n = 23) had an abnormal LCI (>7.0) before commencing HS.

Patients were followed for a mean duration of 6.77 (4.14) months pre and 39.7 (7.40) months post starting HS inhalation. Lung function parameters remained remarkably stable after commencing HS. Compared with the last value before HS therapy, the first LCI values on HS had significantly improved with a mean decline of −0.57 (SD 0.89, p = 0.0007). The mean LCI after three years of treatment was still significantly better than the mean value before therapy (mean change -0.72, SD 0.97, p = 0.0001) (Fig. 1).

To exclude that the halted progression of lung disease had already been present before commencing HS treatment, we evaluated FEV_1 results from the 28 patients who were already old enough to perform spirometry 3 years prior to start of HS. We observed a mean decline in FEV_1 of −3.89% (10.5) predicted within 3 years, although this trend was not statistically significant (p = 0.061). After 3 years of HS inhalation, mean FEV_1 increased by +3.64% (11.5) predicted (p = 0.106). The intraindividual FEV_1 changes during these two periods were significantly different (p = 0.049 in a paired *t*-test), indicating a change in the longitudinal course of the percentage of predicted FEV_1 after starting HS inhalation (Fig. 2).

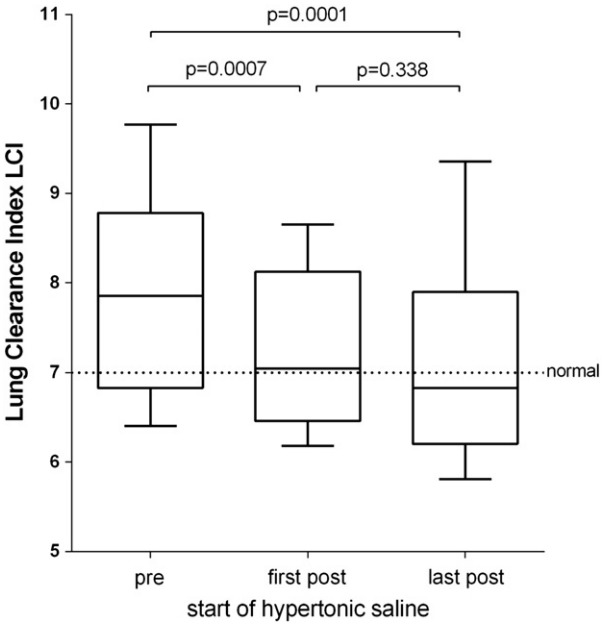

Fig. 1. Boxplots (whiskers: 10th to 90th percentile) of LCI measurements obtained in n = 34 patients over >3 years before and after start of hypertonic saline inhalations. The mean (SD) duration between MBW measurements and start of HS were: Pre −6.77 (4.14) months, first post 6.56 (4.11) months, last post 39.7 (7.4) months, respectively.